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RESEARCH ARTICLE

CATALYTICAL AND ANTICANCER STUDIES OF COMPLEXES OF 2-[(5-METHOXY-1H-BENZIMIDAZOL-2-YL)SULFONYL]-N-PHENYLACETAMIDE WITH ALKALINE EARTH METAL IONS.

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Abstract

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Among carbohydrates, essential amino acids, vitamins, alkaloids, glycosides etc. the presence of heterocyclic structures in such diverse types of compounds strongly indicates that these compounds possess different types of the pharmacological activity. The present work has been done in the search of some potential biochemically active derivatives of 2-mercaptobenzothiazole for medicinal as well as nutritional purposes. Currently used compounds which upon substitution at either functional group or linked with heterocyclic rings or molecules with metal ions, many times, capable of performing better. Synthesis of newer molecules is usually carried out by new linkage through functional groups present in molecules. After the synthetic procedure, the newer molecules require spectroscopic characterization in order to ascertain their structure. In the present work ,2-mercapto 5- methoxy benzimidazolmolecule has been linked with N-(4-acetylphenyl)-2-chloroacetamide heterocycles and instrumental methods like C,H,N,S Analyzer , FT IR spectroscopy, MASS spectrometry, UV spectroscopy etc. have been used for structure elucidation and their important biological activities and also catalytic properties have been studied.

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Introduction:-

The compound 2-[(5-methyl-1H-Benzemidezole–2-yl)sulfonyl]-N- phenyl Acetamide (MBSPA) is the important intermediate required for the synthesis of omeprazole. The reactions were also performed in the presence of phase-transfer catalysts.

Experimental:-

Aniline, toluene, TEA (tri ethylamine), dichloromethane, acetone (all analytical grade)and 2-mercapto-5-methoxy-1H-benzimidazole were used for the preparation of ligand. Mg(II),Ca (II), Sr(II) and Ba(II) perchlorates in DMSO were prepared. The exact strength of 0.2M perchloric acid was determined by pH metric titration against 0.2M NaOH solution (standardized with 0.2N oxalic acid).Metal perchlorates were prepared by mixing solid carbonates

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with perchloric acid solution. To a well stirred solution of 4-methoxy aniline (a) (0.01 mol. 1.23gm) in dichloromethane (0.11 mol. 9.34 gm) acetic anhydride (0.01 mol. 1.02gm) was added drop wise at room temperature in a period of 30 minutes. Organic layer containing N-(4-methoxyphenyl) acetamide (b) (0.01 mol) was taken in a round bottom flask and cooled to 20 -25 0C. To this solution, concentrated sulphuric acid (0.015 mol, 0.8 ml) was added followed by the addition of fuming nitric acid (0.02 mol, 0.88 ml) at 20 – 25 °c in a period of 2 hours. Organic layer was neutralized by 10% NaOH solution. Methanol (8 ml) was added to crude 4-methoxy-2-nitrophenyl) amide (0.009 mol) and the resulting yellow solution was stirred. NaOH (0.027 mol, .1.08gm) was slowly added to it and refluxed at 80 °C. Reaction mass was then stirred at room temperature for another 3 hrs. Organic layer containing 4-methoxybenzene -1,2-diamide (0.008mol) was reduced by adding Na₂S 9H₂O (0.016mol, .84gm) and NaHCO₃ (0.014mol, 1.18gm) and water (6ml). The reaction mixture was refluxed for 5 hours at 80 °C. Organic layer containing 2-mercapto-5-methoxy-1H- Benzimidazole (1.0gm, 0.0072mole) was cooled at 30 °C. To this, NaOH (1.08gm, 0.027mole) was added and stirred at room temperature. CS₂ (1.21gm, 0.016 mole) was added slowly in 1 hrs. at temperature below 30°C. Reaction mass was very carefully heated to reflux for 6 hours. Solvent was evaporated under reduced pressure and reaction mass was acidified to pH=2 by adding 33% hydrochloric acid 4.0gm, 0.036mole).Yield: 72%, 254-255 °C. The organic compound was synthesized out of 11 ml aniline by drop wise addition of 300 ml of the dichloromethane and 25 gm of the potassium carbonate was added then after. Drop wise addition of 25 ml of chloroacetyl chloride was followed. The precipitates obtained were filtered. This product – A (2-chloro-N-phenylacetamide) (25 gm) was dissolved in 300 ml acetone and the compound – B (2-mercapto-5-methoxy-1H-benzimidazole) (18.78 gm) was mixed with it and this mixture was stirred well with 25 gm K₂CO₃ in ice bath. The light white solid [compound C] (2-[(5-methyl-1H-Benzemidezole-2-yl) sulfonyl]-N- phenyl Acetamide) was obtained by addition of cold water and purified to give the ligand MBSPA. The formation of complexes was carried out by mixing 50 ml 0.2 M metal perchlorate solution and 50 ml 0.2 M ligand in DMSO solution. The reaction mixture was refluxed for 2.5 to 3.0 hours at 95 °C temperature. The pH of the above solution was then raised up to 6.5 using with aqueous which resulted in the precipitation of the complex.

Analyses and physical measurements:-

M.P. and TLC were taken with usual apparatus [solvent system for TLC 70% toluene + 30% methanol]. Elemental analyses were performed with a Vario-MICRO CUBE C, H, N, S analyzer. The metal content was determined by titration with a solution of standardized disodium salt of EDTA [1].Magnetic susceptibilities were measured by the Gouy's method [2], at room temperature using Hg[Co(CNS)₄]as calibrant. The IR spectra were recorded on a BRUKER ALPHA FT-IR 400 – 4000 cm⁻¹ spectrophotometer. The UV – visible spectra were measured on a UV-1800 Shimadzu (Double beam) spectrophotometer. Thermal measurements were performed using a METTLER TOLEDO STARe system TGA/DSC1(11500C) thermal analyzer. The mass spectra analyses were performed with a model QDA of Waters and Alliance 2690 analyzer.

Table 1:- Analytical Data and Some Physical Properties of the Ligand and Metal Complexes.

Metal complex	Molar Conductions In DMSO Mili Mhos cm ⁻¹	Rf Value	Color	% of Yield	% of Metal Exp. (calc.)	M.P. 0C	% of C Exp. (calc.)	% of H Exp. (calc.)	% of N Exp. (calc.)	% of S Exp. (calc.)
MBSPA	--	0.368	Cramy white	--	--	173	--	--	--	--
Mg-MBSPA	11.2	0.34	Light Brown	85 %	4.86 (4.86)	160	55.97 (60.45)	4.95 (4.888)	12.24 (12.88)	9.32 (28.269)
Ca-MBSPA	12.0	0.33	Orange	83 %	4.86 (4.86)	110	51.66 (56.90)	5.00 (4.908)	11.66 (12.26)	8.88 (25.105)
Sr-MBSPA	69.3	0.32	Bright Brown	93 %	7.00 (8.9)	152-155	51.2 (56.63)	4.53 (4.474)	11.2 (11.02)	8.53 (24.114)
Ba-MBSPA	10.5	0.35	Dark Bright Brown	82 %	5.49 (9.79)	150	45.98 (57.21)	4.55 (4.846)	10.05 (11.81)	7.66 (26.986)

*Solvent system = toluene (70 %) : methanol (30%), % of (calc.) = calculated, % of metal = By EDTA titration method, Exp. = experimental.

Physico chemical properties:-

Molar conductances of complexes indicate nonionic nature. Rf and melting point values suggest complexes formation. Elemental analyses support the molecular formula that is thought of. However, percentages of sulfur do not agree with the experimental values probably because of some instrumental disturbances.

IR Spectra:-

Infrared spectroscopic technique [3-6] is of an immense importance to organic chemists for the identification of the presence of functional groups as well as carbon skeleton in the organic compounds.

IR (KBr): 3282(N-H Stre.), 1600 (>C=O stre.), 1444 (-C=N stre.), 1075,1114 (Ar-C-H aromatic), 1330-1444 (-CH₂-stre.), 751,750,759,756 (C-S stre., M= Mg²⁺), 417 (M-S stre., M= Ca²⁺, Sr²⁺, Ba²⁺), 478,462,472 (M-O stre.), 673,691,692 (M-N stre.), and 673 (o-di substituted benzene stre.). 1454- (CH₂) Scissoring, 1395- wagging and twisting, 1114 (-C-O-C stre.)- Asymmetric stretching, 1648 (-N-H) in plane bending. All the figures in cm⁻¹.

Mass spectrometry:-

Probably the most common uses of mass spectrometry by the chemist is for the accurate determination of molecular weight as well as structure elucidation.

Mg-MBSPA :- Mass m/z:- Base peak = 314.1 amu, (B. P. +1) is around 13 % of B.P. (314.1) therefore 12 carbon atoms present in the fragment corresponding to base peak and Base peak +2 presence of = confirms presence of sulphur, Thus base peak is due to ligand molecule MBSPA, Base peak+ metal = 337.67 amu, Base peak – Aniline = 221.1 amu, Base peak + Metal = 336.2 amu

Ca-MBSPA:- Mass m/z:- Base peak = 314.1 amu ,(B. P. +1) is around 15 % of B.P. (314.1) therefore 14 carbon atoms present in the fragment corresponding to base peak,,S is present in base peak (314+2) so base peak is pertaining to ligand, Base peak + Metal = 353.44 amu, Base peak – Aniline = 221.1 amu

Sr-MBSPA:- Mass m/z:- Base peak = 314.1 amu, (B. P. +1) is around 12 % of B.P. (314.2) therefore 11 carbon atoms present in the fragment corresponding to base peak, Presence of 'S' indicated by (base peak + 2). Thus base peak is due to ligand molecule.,Metal + base peak = 400.99 amu, Base peak – Aniline = 221.1 amu

Ba-MBSPA:- Mass m/z:- Base peak = 314.1 amu, (B. P. +1) is around 15 % of B.P. (314.1) therefore 14 carbon atoms present in the fragment corresponding to base peak is due to the ligand molecule. Base peak – Aniline = 221.1 amu, Metal + base peak– N-Ph = 317.7 amu.

Magnetic moments:-

The magnetic moments of the complexes were measured by the Gouy's method. The room temperature magnetic moment of the solid complexes was found to be Diamagnetic.

Table 2:- Electronic spectra and Magnetic properties

N0.	Brief name of complex	Formula	Molecular weight Gm/mol	Electronic Spectra	Magnetic moment (B.M.)	Pascale's Diamagnetic correction erg.G-2mol-1
				Nm → cm-1		
1.	Mg-MBSPA	$[\text{Mg}(\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{S})_2(\text{H}_2\text{O})_2]$	86	300.50→33277 253.50→39447 241.50→41407 231.50→43196 228.50→43776 218.50→45766	Diamagnetic	-372.44x10-6
2.	Ca-MBSPA	$[\text{Ca}(\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{S})_2(\text{H}_2\text{O})_2]\text{H}_2\text{O}$	720	300.50→33277 255.00→39215 231.50→43196 221.00→45248	Diamagnetic	-388.31x10-6
3.	Sr-MBSPA	$[\text{Sr}(\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{S})_2(\text{H}_2\text{O})_2]$	750	305.50→32733 255.00→39215 239.50→41753 220.00→45454	Diamagnetic	-383.44x10-6
4.	Ba-MBSPA	$[\text{Ba}(\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{S})_2(\text{H}_2\text{O})_3]\text{H}_2\text{O}$	835	302.00→33112 256.00→39062 244.50→40899 228.00→43859 221.00→45248 209.00→47846	Diamagnetic	-314.1x10-6

Electronic spectra and Magnetic properties:-

The alkaline earth metals are usually diamagnetic due to absence of unpaired electrons. The organic ligand is also diamagnetic. Measurements of magnetic susceptibilities helps to observe any paramagnetism present like TIP or spin-orbit coupling. In all the four cases complexes were found to be diamagnetic. Likewise, due to absence of d-d transitions in alkaline earth metal ion complexes, not much information could be obtained except charge transfer transitions.

Thermo gravimetric analysis:-

Thermo gravimetric analysis (TGA) can provide about physical phenomena, such as second-order phase transitions, including vaporization, absorption, sublimation, adsorption and desorption. chemical (especially dehydration), decomposition and solid gas reactions (e.g., oxidation or reduction)[7] TGA is commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation or loss of volatiles (such as moisture).

Differential scanning calorimetry is a technique determining the variation in the heat flow given out or taken in by a sample.

Table 3:- Thermo gravimetric analysis

Compound	RT - 150 °C			150 °C - 250 °C		
	% weight loss	% Loss of weight(gm) for 1 mole complex	water molecules	% weight loss	% Loss of weight(gm) for 1 mole complex	water molecules
Mg-MBSPA	4.7	4.95	0	12.83	43.25	2
Ca-MBSPA	3.18	11.24	1	9.47	33.44	2
Sr-MBSPA	0.80	3.24	0	8.83	35.41	2
Ba-MBSPA	3.33	15.02	1	12.36	55.63	3

RT = Room temperature.

Based upon the results of physicochemical analyses their probable structures are as shown in figures below.

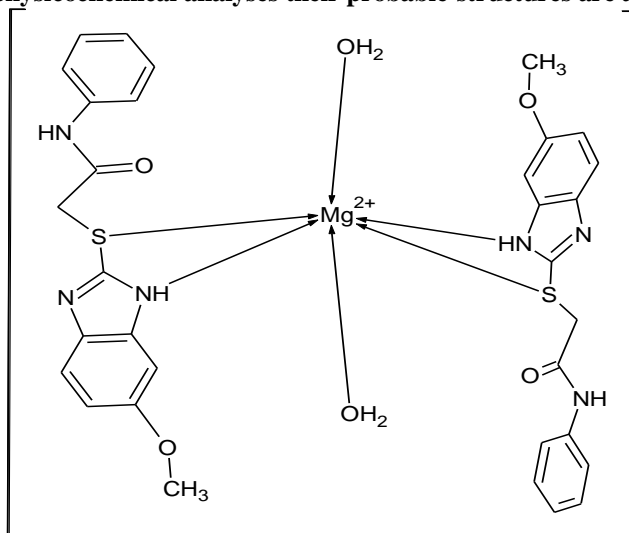


Figure 1:- Mg-MBSPA Structure

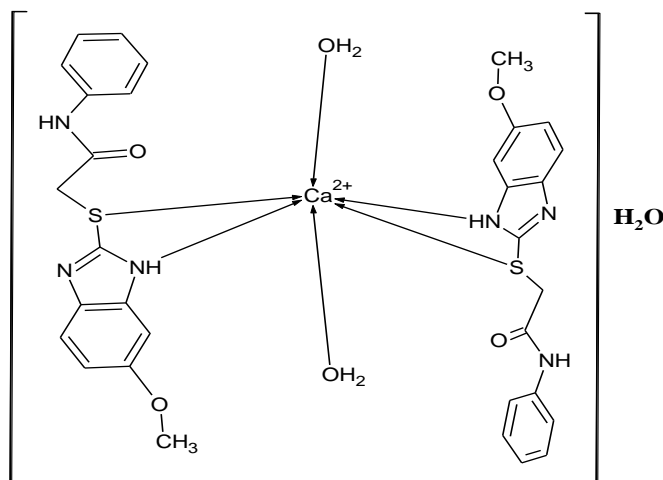


Figure 2:- Ca-MBSPA Structure

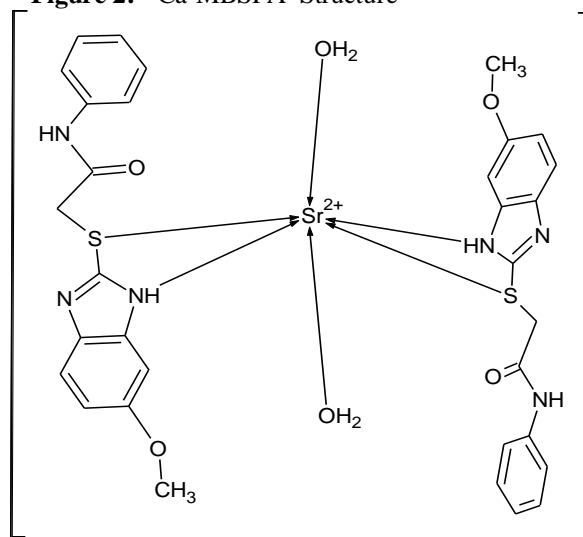


Figure 3:- Sr-MBSPA Structure

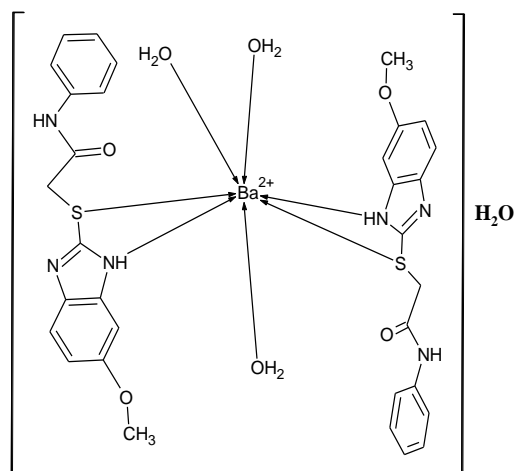
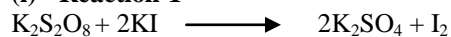
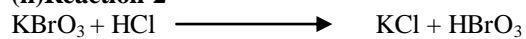
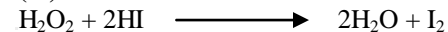


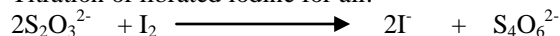
Figure 4:- Sr-MBSPA Structure

Chemical kinetics:-

Three reactions (i) $K_2S_2O_8 + KI$ (ii) $KBrO_3 + KI$ and (iii) $H_2O_2 + KI$ were selected. These reactions are usually carried out in neutral or acidic medium. The reactions are such that they proceed with moderate velocity $K = 10^{-2}$ to 10^{-5} per minute. The product of all these reactions is iodine which is titrated with standard aqueous sodium thiosulphate. The rates of all these reactions can easily be measured by simple kinetic methods therefore one of the important applications of coordination compounds, as catalysts, is being investigated [8].

Reactions:-**(i) Reaction-1****(ii) Reaction-2****(iii) Reaction-3**

Titration of liberated iodine for all:

**Catalysis of Organic Reaction:-**

Azoxybenzene is an azo compound, it gives a substitution reaction. Azoxybenzene also gives intra molecular rearrangement in presence of concentrated H_2SO_4 . It reduces to give azobenzene. It can be prepared by boiling with methanol in alkaline medium. Methanol is oxidized to formic acid while nitrobenzene is converted to Azoxybenzene.

Table 4:- Overall results of catalytic activity for complexes of Alkaline earth metals.

Reactions	k without complex	k with (1%) Mg-MBSPA	k with (1%) Ca-MBSPA	k with (1%) Sr-MBSPA	k with (1%) Ba-MBSPA	% Increase in reaction rate at T = 300 K for Mg-MBSPA	% Increase in reaction rate at T = 300 K for Ca-MBSPA	% Increase in reaction rate at T = 300 K for Sr-MBSPA	% Increase in reaction rate at T = 300 K for Ba-MBSPA
$K_2S_2O_8 + KI$	2.085×10^{-5}	9.96×10^{-6}	7.44×10^{-6}	6.91×10^{-5}	9.08×10^{-6}	-52.23*	-64.31*	231.41	-56.45*
$KBrO_3 + HI$	1.44×10^{-3}	2.12×10^{-3}	1.73×10^{-3}	1.78×10^{-3}	1.78×10^{-3}	47.22	20.13	23.61	23.61
$H_2O_2 + HI$	6.78×10^{-5}	3.47×10^{-4}	4.06×10^{-4}	3.52×10^{-4}	3.44×10^{-4}	411.79	498.82	419.17	407.37

*Decrease in the reaction rate

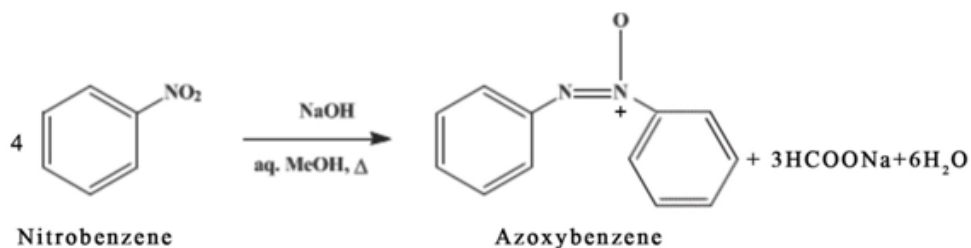


Figure 5:- Reaction of Azoxybenzene

As per the literature, for this reaction, 23gm of sodium hydroxide is added to a solution of 15 ml of nitrobenzene in 120 ml of methanol. After 3 hours refluxing orange coloured solution is observed. Then after methanol is distilled as much as possible. After that the reaction mixture is poured in cold water and mixture is made acidic with HCl. The crude azoxybenzene is separated by the separating funnel. The bottom organic layer is collected which solidifies at around 1°C to 2°C.[9]

Table :- 5 Percentage yield with catalyst alkaline earth metal complex

	Product Weight without metal complex (3 hours)	Product Weight without metal complex 2 hours	Product weight using Mg-BSPA as catalyst 2 hours	Product weight using Ca-MBSPA as catalyst 2 hours	Product weight using Sr -MBSPA as catalyst 2 hours	Product weight using Ba-MBSPA as catalyst 2 hours
Weight in gram	7.93	4.95	6.10	6.20	5.90	6.25
% yield	86.19%	60.36%	74.39%	75.60%	71.95%	76.21%

(% yield for 0.05 % catalyst addition)

Result and Discussion:-

The Azoxybenzene formation reaction is a well known and important reaction. This is usually carried out for a time period of three hours to yield product. When this reaction is carried out for two hours, 60.36% yield was obtained. On application of 0.05% of alkaline earth metal ion complex with MBSPA ligand, the rate of reaction increased as a consequence, percentage yield also increased. The catalytic efficiency observed is, Ba-MBSPA > Ca-MBSPA > Mg-MBSPA > Sr-MBSPA.

Antibacterial activity:-

This part deals with the in-vitro screening of newly prepared compounds for antibacterial activity. The species *S.aureus*, *E.coli*, *S.Pyogenes* and *P.Aeruginosa* have been taken for the antibacterial activities. Agar-cup method was employed for the in-vitro screening for antibacterial activity.[10]

Table 6:- Standard drugs.

Culture	Well No.
<i>Bacillus sp.</i>	++
<i>Staphylococcus aureus</i>	+++
<i>E. coli</i>	+++
<i>Salmonella typhi</i>	+++

Table 7:- Antibacterial activity of MBSPA and alkaline earth metal complexes

Culture	Well No.	Compounds Name			
		Mg-MBSPA	Ca-MBSPA	Sr-MBSPA	Ba-MBSPA
<i>Bacillus sp.</i>	4 (100 µg/ml)	+	-	-	+
	3 (200 µg/ml)	+	+	-	++
	2 (300 µg/ml)	+	++	-	++
	1 (400 µg/ml)	+++	++	-	+++
<i>Staphylococcus</i>	4 (100 µg/ml)	+	-	-	-

<i>aureus</i>	3 (200 µg/ml)	+	+	-	-
	2 (300 µg/ml)	+	+	+	+
	1 (400 µg/ml)	++	+	+	+
<i>E. coli</i>	4 (100 µg/ml)	-	+	-	-
	3 (200 µg/ml)	+	+	-	+
	2 (300 µg/ml)	+	+	+	+
	1 (400 µg/ml)	++	+	+	+
<i>Salmonella typhi</i>	4 (100 µg/ml)	-	-	-	-
	3 (200 µg/ml)	-	+	+	-
	2 (300 µg/ml)	+	+	+	-
	1 (400 µg/ml)	++	++	++	+

Zone Size:+++ 2.6 to 3.0 cm Streptomycin (25 µg/disc) for *E. coli*, *S. typhi* & *S. aureus*++ 2.0 to 2.5 cm Ampicilin (25 µg/ml) for *Bacillus sp.*+ 1.0 to 1.9 cm Ketoconazole (10 µg/ml) for Yeast and *Aspergillus*

- No zone Well Size is 0.8 cm

Comparison of antimicrobial activity of synthesized compounds with that of standard antimicrobial drugs reveals that the complexes show moderate to good activity against all four bacterial strains, however by and large lower than the standard.

Antifungal activity:-

This part deals with the in-vitro screening of newly prepared complexes for antibacterial activity. The species *C. albicans*, *A. niger*, *A. clavatus* have been taken for the antifungal activities. Here too, the Agar-cup method was used for the in-vitro screening for antifungal activity. [11,12]

Table 8:- Standard drugs.

Yeast	+
<i>Aspergillus</i>	+

Table 9:- Anti fungal activity of MBSPA and alkaline earth metal complexes.

Culture	Well No.	Compounds Name			
		Mg-MBSPA	Ca-MBSPA	Sr-MBSPA	Ba-MBSPA
Yeast	4 (100 µg/ml)	-	-	-	-
	3 (200 µg/ml)	-	-	+	-
	2 (300 µg/ml)	-	-	++	-
	1 (400 µg/ml)	+	-	++	+
<i>Aspergillus</i>	4 (100 µg/ml)	-	-	-	-
	3 (200 µg/ml)	-	-	-	-
	2 (300 µg/ml)	-	+	-	-
	1(400 µg/ml)	+	+	+	+

+ 1.0 to 1.9 cm Ketoconazole (10 µg/ml) for Yeast and *Aspergillus*

- No zone Well Size is 0.8 cm

Comparison of antimicrobial activity of complexes with that of standard antimicrobial drugs reveals that the synthesized complexes show moderate to good activity against all three fungal strains.

Anticancer activity:-

To study cytotoxic activity of a compound, cytotoxic assays are carried out. It is now well-documented that apoptosis or programmed cell death is the key mechanism by which Chemotherapeutic agents exert their cytotoxicity.

Result and Discussion:-

In the present investigation, all the compounds were evaluated against various cell lines named MDA-MB-468, VERO (Normal Cell) and HCT-15 for each tested compound as well as Std. anticancer drug Methotrexate, Dose Response Curve (DRC) against all cell lines was plotted with 10 analysis point i.e. with 10 different drug concentrations. The concentration causing 50% cell growth inhibition (IC₅₀) was determined from DRC using GraphPad Prism software (Ver. 5.04) (GraphPad Software, Inc., USA) and Microsoft Excel 2007 (Microsoft Corporation, USA) application.

Amongst all the tested compounds, for MDA-MB-468 cell line compound Ca-MBSPA (IC₅₀ value 42.98 µg/ml) both were giving potent inhibitory effect under studied cell line. While, Ba-MBSPA (IC₅₀ value 91.70 µg/ml), Sr-MBSPA (IC₅₀ value 94.08 µg/ml) gives good effect on said cell line. Similarly for HCT-15 cell line, Ca-MBSPA and Ba-MBSPA were found to be potent against Human colon cancer cell line. Normal cell study was under taken by using VERO cell and study was indicated that Ca-MBSPA was found to be toxic to normal cell. So, one cannot used for further mechanism based study. While rest of compounds can go for further mechanism based study by selecting their potential IC₅₀ values for inhibition. Then after, one can go for further *in vivo* study of the non-toxic compounds series for detail mechanistic study using Tunnel assay, Flow cytometry, DNA fragmentation assay Or CASPACASE assay.

Conclusion:-

From above all the results, it can be concluded that compounds Ca-MBSPA and Ba-MBSPA give good cytotoxic activity on MDA-MB-468 cell lines (i.e. Human Breast cancer Cell line). While Ca-MBSPA and Ba-MBSPA compounds show potent activity on HCT-15 cell lines (Human Colon Cancer). When normal cell comparison study was carried out, it was proven by study that compound Ca-MBSPA was toxic to normal cell. All results were compared with standard anticancer drug Methotrexate using IC₅₀ values for all three cell lines.

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